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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDREW PAUL CHAPMAN and DAVID JOHN KING

Appeal 2008-0454
Application 09/719,045
Technology Center 1600

Oral Hearing Held: April 17, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

ON BEHALF OF THE APPELLANT:

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P R O C E E D I N G S

MS. BEAN: Good morning.

JUDGE LEBOVITZ: Good morning.

JUDGE SCHEINER: Good morning.

MS. BEAN: Calendar Number 49, Mrs. Trujillo.

JUDGE SCHEINER: Thank you.
MS. BEAN: You're welcome.
JUDGE SCHEINER: Good morning.
MS. TRUJILLO: Is there any? There's nothing in there.
JUDGE SCHEINER: Oh, no. We can get some.
MS. TRUJILLO: That would be helpful, if not --
JUDGE SCHEINER: Of course they're not there.
JUDGE GREEN: They're behind you.
JUDGE SCHEINER: Oh. In here?
JUDGE LEBOVITZ: It's somewhere, take a look for it.
MS. TRUJILLO: Sorry.
JUDGE SCHEINER: That's all right.
JUDGE LEBOVITZ: Well, I see a box, but it's empty.
JUDGE SCHEINER: Let's see. All right, well, we can call the usher in and have some put in here.
MS. TRUJILLO: That's okay.
JUDGE SCHEINER: Other than --
MS. TRUJILLO: Oh, wait, they're here.
JUDGE SCHEINER: Oh, okay, great.
MS. TRUJILLO: Sorry. It was right here all along.
JUDGE SCHEINER: All right. Well, whenever you're ready, you'll have 20 minutes. I should point out this clock here is not working, so don't go by that.
MS. TRUJILLO: Okay.
JUDGE SCHEINER: We just noticed it this morning.

MS. TRUJILLO: Now, I don't think I need --

JUDGE SCHEINER: No, you don't have to --

MS. TRUJILLO: I don't think we need to worry about. Is -- so the Examiner, I don't need to reserve rebuttal. He's not attending.

JUDGE SCHEINER: No.

MS. TRUJILLO: Okay.

JUDGE SCHEINER: Were you told otherwise, because --

MS. TRUJILLO: No --

JUDGE SCHEINER: -- normally --

MS. TRUJILLO: I didn't know. I didn't know --

JUDGE SCHEINER: Okay --

MS. TRUJILLO: So, I just thought --

JUDGE SCHEINER: -- normally we're informed too if the Examiner has asked to attend, but --

MS. TRUJILLO: Okay.

JUDGE SCHEINER: -- we didn't hear anything, so --

MS. TRUJILLO: All right. May it please the Board, I'm Doreen Trujillo from Cozen O'Connor. I am representing the Applicants Chapman and King regarding Application Serial Number 09/719,045. The title of the Application is Divalent Antibody Fragments.

Now what Applicants are claiming in the application on appeal, as mentioned in the title, is a Divalent Antibody Fragment, but the fragment isn't just an antibody fragment, it's been modified with a polymer in a very specific way. And if you look at Claim 1 from which all the other claims depend, the claim specifies exactly where the polymer is to be attached.

And, if I may go over -- basically, the claim specifies that the Divalent Fragment, and divalent, basically, means of course, that there are two antigen binding domains, has at least two heavy chains with a variable region and a portion of the constant region and has two cysteine residues that are outside the variable region. Here are the variable, your constant.

Each chain has assisting region outside the variable domain that is involved in an interchain bridge, meaning a bridge between the two heavy chains, and that the interchain bridge is the polymer molecule. So, specifically, the claim recites that you have a divalent fragment that has its inner chain -- one of the interchain bridges not affected by a disulfide bond, but instead affected by the polymer molecule, and it's very, very specific that that's where it's to be located.

The example that's provided in the specification, the working example which was used to make the divalent fragment used what are called Fab'. Two Fab's were added to the polymer molecule to make the example provided.

JUDGE LEBOVITZ: Is Fab' the one with hinge region?

MS. TRUJILLO: Yes, and I'll go into that a little bit more as well. Yes, it has a little bit of the hinge, but it's not required in the claim that --

JUDGE LEBOVITZ: Right.

MS. TRUJILLO: -- it be Fab', but just that it have a Cysteine outside the variable domain in order to affect that interchain bond.

Now, the reason that we're so specific where the polymer is attached is because Applicants found a way to attach the polymer without sacrificing

antigen binding efficacy, and because in the art, some of the art, they didn't specify where it should be attached and didn't focus on antigen binding.

JUDGE LEBOVITZ: But, let me just ask a question: This does say a divalent antibody fragment, and you were just talking about it having, you know, conserving the binding efficacy, but it doesn't require a light chain --

MS. TRUJILLO: It --

JUDGE LEBOVITZ: -- or would that be required by divalent antibody fragments?

MS. TRUJILLO: There are some -- I'm sorry, there are some heavy chain-only antibodies that combine just with a heavy chain.

JUDGE LEBOVITZ: Okay.

MS. TRUJILLO: It doesn't require it, but yes, presumably it would have in many instances the light chain as well.

Now, just to give a little history, it's kind of like the story of Goldilocks. The reason that we got to divalent antibody fragments with polymers is because when people first started using antibodies in vivo for diagnostics or for therapy, they had -- they found that their circulating time in the body was a little too long and caused problems with background for diagnosis and also binding to healthy cells for therapy because antibody molecules are so big. They're about 150,000 molecular weight.

So, they were looking for an alternative because they stayed around too long, and when it came -- they developed fragments, ways to fragment the antibodies and still have antigen binding, they learned that the fragments were too small. So, the antibody, the whole antibody was too big, and the fragments were too small so they looked for something intermediate, and

that's where they came up with adding polymers which would give the fragments a large effective size. But, as I said, at first they weren't really focusing upon where they were attaching them. And -- leave that over here.

So, if you have a whole antibody -- so here's -- again, the heavy chains are the longer chains, and the light chains, they're attached. When they first did the fragments, they used enzymes to digest the antibodies. One enzyme was papain, and it digested above this heavy chain disulfide bridge. So, you ended up with two monovalent Fab fragments from the two original heavy chains and light chains. That was papain. But, when they used another enzyme, Pepsin, this would digest below the disulfide bridge so you'd end up what, with this whole thing was called an Fab' sub2. So, it would be basically contained still the bridge, and if you were to reduce that, you would end up with two Fab's.

JUDGE LEBOVITZ: We're pretty familiar with --

MS. TRUJILLO: Okay, I --

JUDGE LEBOVITZ: -- the -- biology.

MS. TRUJILLO: Yeah, just stop me --

JUDGE LEBOVITZ: So, we should get -- let's talk about Gonzalez then.

MS. TRUJILLO: Okay. So the reference is cited against the Applicants as you raised is the Gonzalez Patent. The reason I went into that is because I think it's very important --

JUDGE LEBOVITZ: Correct.

MS. TRUJILLO: -- part of the Examiner's rejection. The Gonzalez Patent was cited for both rejections. There are two rejections: an

anticipation or, in the alternative, obviousness rejection and over Gonzalez alone, and then an obviousness rejection over Gonzalez in view of Barbanti.

And, I could see the offices in the Examiner's frustration with Gonzalez because if you've seen the reference, I brought it here, it's like about one or two pounds. There are 206 columns, 136 drawings. Surely, somewhere in this reference there must be a disclosure of what Applicants are claiming, but unfortunately, there is not.

Gonzalez does have a lot of disclosure, does have discussion regarding polymers, does have discussion regarding Fab', Fab' sub2, but what Gonzalez doesn't have is a disclosure, again, going back to the Applicant's claim which it requires that the polymer essentially function as the interchain bridge between two cysteines outside the variable domain on the heavy chain.

JUDGE LEBOVITZ: But, doesn't Gonzalez tell you in Column 19 that the Examiner pointed to that putting the polymers such as PEG in the hinge region, hinge region of an Fab fragment is one of -- is a preferred embodiment?

MS. TRUJILLO: Yes, it does, and that, and that's talking about using the monovalent, the Fab', and it talks about attaching it to the hinge, and it even has an embodiments where it's using the Fab' attached to the hinge, but then when you look at other discussion with when it's a divalent, the discussion were, the Examiner relies on the citation to the dumbbell shape where you have one polymer with two antibodies attached. There's no discussion about where, where it should be attached. It doesn't specify that you should attach it to the particular cysteine. There are various -- it

discloses other points of attachment, other amino acids, lysine, other -- so it's not necessarily the only place of attachment.

In terms of the monovalent Fab', it does mention hinge, but --

JUDGE SCHEINER: But, they do talk about in the preceding paragraph on Column 35 up top of putting it on a hinge region.

MS. TRUJILLO: I'm sorry.

JUDGE SCHEINER: On, on Column 35 of Gonzalez, they do talk about putting -- the PEG molecule being attached to the hinge region.

MS. TRUJILLO: Right, but it's monovalent. When they talk --

JUDGE SCHEINER: But, then they say in other embodiments -- I mean, if you're going to read those two paragraphs together, I think an ordinary artisan would get out of it that you could put this on the hinge region and get a dumbbell shape.

MS. TRUJILLO: Okay. Well, the problem is when you read the whole reference, again, it doesn't specifically point you to that. It's talking mainly about the monovalent, and basically it doesn't specifically disclose that. So perhaps you can say it could lead you to that, but that's not anticipation.

JUDGE LEBOVITZ: Well, Number 1, the Examiner does say anticipation or, alternatively, obviousness.

MS. TRUJILLO: Right.

JUDGE LEBOVITZ: At Number 2 since you draw on it, how else would you draw a dumbbell shape if it --

MS. TRUJILLO: Well, it could be any way. I mean, they don't really describe it, and they specifically state -- and this is the thing that

we've had a problem with all along. If you're not in an anticipation, then you have to consider what Gonzalez is saying about the Fab' 2. And whenever they're talking about using the cysteine, it always mentions whether it's the cysteine between heavy and light chain or the cysteine between heavy chains.

Gonzalez specifies that the other cysteine should be changed so that their polymer isn't working as an interchain bridge between the two chains.

JUDGE LEBOVITZ: Well, what the -- no, I mean, what in that example -- you know, we agree that they do say when you're in certain Fab fragments, when you're connecting the light chain to the heavy chain you would attach the polymer to a cysteine on one chain and then the other chain you would remove the cysteine there, but you'd still have a bridge so the cysteine, would still be in -- at least one cysteine would still be involved in the bridge.

MS. TRUJILLO: Right, but they specifically state when it's, as I said, not only between the heavy and light chain but the heavy and heavy chain for the Fab' 2 that you always make sure that the other amino acid is not a Cysteine so that it doesn't form the covalent bond as required in our claims. And that's been -- as I said, that's been our argument all along.

If you look at Column 21, Lines 50 to 60, in yet another embodiment the conjugate contains an Fab' sub2 wherein every polymer molecule is attached to a Cysteine residue in the light or heavy chain of the antibody fragment that would ordinarily form the disulfide bridge linking the light and heavy chains, wherein the disulfide bridge is avoided by substituting another

amino acid such as serene for the corresponding Cysteine residue in the opposite chain.

JUDGE LEBOVITZ: But, what about the Examiner's argument that -- I think on Line -- Columns 120 to 122, the example he gives you the patent describes the exact chemistry for putting a polymer on a Cysteine residue.

MS. TRUJILLO: But, it's a different procedure. If you read the procedure then from what we do, they recite that you have the Fab' and five moler equivalents of the polymer. When you read our procedure, we have a moler ratio of the Fab 2.2 to 1, to the polymer.

JUDGE LEBOVITZ: But, that's not in the claim, correct?

MS. TRUJILLO: Right, that's not in the claim.

JUDGE LEBOVITZ: Okay.

MS. TRUJILLO: But, if you're arguing inherency, if you're trying to say Gonzalez would get to that eventually, Gonzalez has -- even though they did that procedure, they don't -- they give the example and, and the gel, the SDS gel, there's nothing about a divalent fragment. They didn't come up with a divalent and a body bound to the polymer. So, that's basically been our argument all along. One thing that the Examiner argued was, well yeah you're not starting out with a divalent Fab' sub2, you're starting with a Fab' in your example.

Again, we're not limited to that. But even though we're starting out with the Fab', we're virtually ending up with the same thing that they tell you not to make because we're back to -- we're combining the Fab's with

the polymer as the bridge and we're ending up with exactly what Gonzalez tells you not to end up with, is an Fab' 2 with a polymer bridge.

JUDGE LEBOVITZ: Well, he -- but the -- Gonzalez does say if you've got a hinge region there then he tells you, you can put a Cysteine, you can put a PEG onto the Cysteine in the hinge region and then on Column 1, Line 40, it does say that PEG attached to a sulfhydryl group in the hinge region of the Fab' fragment has reduced clearance. So, based on that, based on those two things, a skilled worker reading it, wouldn't they be invariably led to putting the PEG on the hinge and also when you want to create a divalent hooking them up through the polymer on the hinge?

MS. TRUJILLO: That's -- our argument has been in view of this specific discussion of, of voiding the interchain bridge when you have a divalent that it might but for that, and you have to consider the whole reference. And it -- every time it talks about the interchain bridge with the cysteines between the light chain or the heavy, and heavy chain or the heavy chain and heavy chain, it specifies that the statement that I just read to you previously, is that you change the Cysteine in the other chain so that the interchain bridge is avoided.

And, so that's been our, our argument all along has been if you're not in -- it doesn't anticipate and it doesn't because it doesn't disclose the particular structure that we're claiming. Then, if you're looking at obviousness you have to consider the whole reference. And, the part of the reference that's discussing divalent antibody fragments, regardless of how you get there, is purposely stating that it does not want an interchain bridge. And, when you look at Gonzalez, it makes sense because their polymers are

gigantic. I mean, they're suggesting polymers of 100,000 molecular weight and higher because they were focusing upon just making it bigger, making it appear bigger, so they weren't even looking at antigen binding. They weren't considering antigen binding or anything else. And, so they didn't, they purposely said, keep that interchain bridge from, from forming. So, that's, that's been our argument.

JUDGE LEBOVITZ: Well, the interchain bridge forms -- I think the difference is it only has one sulfur in there. I mean, there is -- they've got to hook the light -- they are talking about hooking the light chain to the heavy chain. What they're, what they're talking about is a production problem, I suppose, they don't explain it that perhaps if you had both cysteines present, you might preferably get a bridge warming before attaching the PEG to it, but they actually do have inner change, inter chain bridge there.

JUDGE SCHEINER: Where it says in every polymer molecule is attached to a Cysteine residue that would ordinarily form the disulfide bridge. So --

JUDGE LEBOVITZ: The disulfide, right.

MS. TRUJILLO: Right.

JUDGE LEBOVITZ: Not, not --

MS. TRUJILLO: And, that's the bridge --

JUDGE LEBOVITZ: Not an interchain bridge.

MS. TRUJILLO: Well, they don't want, right, but, but that's what I'm referring to when I said the interchain bridge, it's the disulfide bridge normally that's holding the two heavy chains together for the divalent or the heavy and light chain together. And, they say wherein the disulfide bridge is

avoided by substituting another amino acid such as serene for the corresponding Cysteine residue in the opposite chain.

So, it's not even where -- as we specify, where we specify that the polymer is attached to cysteines on each heavy chain an the polymer is the interchain bridge, Gonzalez is saying, no, I don't want the polymer to be involved in an interchain bridge in a divalent antibody fragment.

And, then we addressed, I guess, anticipation in the genus species of course and even under KSR under an obvious to try standard, you know, there has to be a finite number and as I stated, you know, these, it could be attached anywhere. There are 110 amino acids on the, the full chains, so they don't really specify. There's not really a lot of guidance and including the teaching away of avoiding the bridge between the two chains, it, it's been our position and we maintain that Gonzalez does not anticipate and does not render obvious Applicant's snippets claims.

And, then regarding Barbonti, Barbonti is specifically related to the TNF alpha, the particular antigen and it describes using the whole antibody against the antigen and then it mentions that fragments can be used, but there's no mention of any problems or issues. The Examiner did raise, you know, that basically said that his standard was it would only have been a person having less than ordinary skill in the art who would've not been motivated to extend the half life of an antibody that is being administered for the purpose of neutralizing an inflammatory molecule such as TNF's alpha. Well, this really isn't the proper standard.

The proper standard is would a person of ordinary skill have been motivated. So, I think the Examiner kind of cites dept the whole burden

there by making conclusionary statement that only a person who wasn't of ordinary skill wouldn't have done so. And, even after KSR, this is something that, that's not allowed. So, again, Applicants maintain that their claim which specifies that the polymer is to be attached in the specific location to cysteine residues on each heavy chain is not disclosed or suggested by Gonzalez.

JUDGE SCHEINER: Just one more question from me. I don't know if other, but I just caught a paragraph out -- granted it's out of context. In Column 41 --

MS. TRUJILLO: Okay.

JUDGE SCHEINER: Starting at about Line 35, and as I said, it's out of context. I haven't read it with, in conjunction with the other parts, but it says that in one embodiment polymer contains only a single group which is reactive this helps to avoid cross linking of protein molecules, however, it is within the scope herein to maximize reaction conditions to reduce cross linking or to purify the reaction products through gel filtration in other -- blah, blah, blah --

MS. TRUJILLO: Right.

JUDGE SCHEINER: In other embodiments, the polymer contains two or more reactive groups for the purpose of linking multiple antibody fragments to the polymer back from --

MS. TRUJILLO: Right again --

JUDGE SCHEINER: Okay, so how is that --

MS. TRUJILLO: -- that's similar to the dumbbell. It doesn't tell you where --

JUDGE SCHEINER: Where, but --

MS. TRUJILLO: It doesn't specify.

JUDGE SCHEINER: But, they are deliberately linking to -- I mean, how does this paragraph play into --

MS. TRUJILLO: I view it as the dumbbell paragraph. It's telling you, okay, you can attach this, but then you look at the specific disclosure saying, but we don't want it to be between two cysteines and form an interchain bridge. So, it's saying yeah, you can use this; you can use the polymer --

JUDGE SCHEINER: Well, how else would you envision the -- I mean, I understand that there are many cites where you can link these, but do we agree that that dumbbell implies a --

MS. TRUJILLO: No.

JUDGE SCHEINER: -- no, no, I'm no saying that implies a symmetrical structure.

MS. TRUJILLO: I'm not going to --

JUDGE SCHEINER: Bilaterally symmetrical structure.

MS. TRUJILLO: -- I, I, I'm sorry; I'm not going to agree because I think that that statement is just kind of thrown out there. In a typical, I mean, this, this patent is no longer even -- it's expired because they stopped paying the maintenance fees, so it's just kind of like -- I think it's a statement that's thrown out there and you're reading into it because in base -- if you didn't have our claims saying that we're have two heavy chains and it's connected by the polymer is the interchain bridge, you, you wouldn't necessarily think of it being there, and then if you -- even without

ours, you have the disclosure in Gonzalez stating, yeah but if you have divalent fragments we don't want the polymer to be the interchain bridge, and I -- as I said, that's been our position all along. You can't ignore that. You have to consider the whole reference. You -- I've, I've highlighted the exact statement you said, but in my view it's the same thing as the dumbbell. It's not telling you exactly where.

JUDGE SCHEINER: Okay. All right, I don't have anything further. Do you?

JUDGE LEBOVITZ: No, I'm okay.

MS. TRUJILLO: Thank you, very much.

(Whereupon, the proceedings concluded at on April 17, 2008)